Liver X receptors in cardiac hypertrophy

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Chapter 6

Relation of Adiponectin and Metformin to Left Ventricular Function after Myocardial Infarction

Data from the Glycometabolic Intervention as adjunct to Primary Coronary Intervention in ST Elevation Myocardial Infarction (GIPS-III) trial

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ABSTRACT

Background. Adiponectin is an adipokine and its levels are reduced in obesity, diabetes, and prevalent heart disease. However, the association between adiponectin and cardiovascular disease is complex, and studies have reported contradictory results. This study sought to investigate the relationship among adiponectin, metformin treatment, and left ventricular function in a substudy of the GIPS-III trial.

Methods. The GIPS-III trial was a randomized, double-blind, placebo-controlled trial in 380 patients who underwent primary percutaneous coronary intervention (PCI) for a first time MI. The aim was to evaluate the efficacy of 4 months metformin treatment on preserving left ventricular function post-MI in non-diabetic patients. Of 380 patients, 308 samples (mean age 58 ± 11 years, 79% male) were available for plasma adiponectin measurement at both baseline and at 4 months.

Results. Median adiponectin level was 5,057 ng/ml (IQR: 3,325-7,596) at baseline and 4,643 ng/ml (IQR: 2,768-6,867) after 4 months. Patients with above median adiponectin levels were more often female (P<0.001). Adiponectin correlated negatively with BMI scores (P=0.007) and creatinine (P=0.043), and showed a positive relationship with NT-proBNP levels (P<0.001) and diastolic blood pressure (P=0.002). Circulating adiponectin levels did not significantly associate with left ventricular ejection fraction (LVEF) or infarct size. Placebo and metformin groups were well-balanced and metformin treatment had no effect on plasma glucose levels. We observed a significant lowering of adiponectin levels following 4 months of metformin treatment compared to placebo (-629 versus -166, respectively; P=0.026).

Conclusion. Treatment with metformin lowered circulating adiponectin levels. Our results do not support a protective role for adiponectin in the preservation of LVEF following MI.

INTRODUCTION

Coronary artery disease (CAD) and myocardial infarction (MI) are prevalent and account for substantial morbidity and mortality in the western world. In the last decades, risk factors for CAD and MI have been identified, and effective treatments have been developed that target and modify these factors, such as anti-hypertensive and lipid lowering drugs. However, important and emerging risk factors are obesity and metabolic syndrome that are not only associated with the pathogenesis of cardiovascular disease, but also implicated in new onset heart failure, and are currently not adequately targeted.

Adiponectin is the most abundant adipokine secreted by adipocytes and has established insulin-sensitizing effects and anti-atherogenic capacity, as well as direct cardioprotective properties, including protection against ischemic, apoptotic, and hypertrophic factors (1,2). Evidence from epidemiological studies implicate a favorable cardiovascular risk profile with high adiponectin. Low concentrations of adiponectin have been observed in obesity (3), type II diabetes (4), and metabolic syndrome (5), and further, are associated with increased risk for CAD (6,7) and myocardial infarction (8,9). Moreover, elevated adiponectin levels in healthy, middle-aged individuals correlated with improved left ventricular (LV) structure and function (10-12), supporting the notion that adiponectin affords cardioprotection. However, paradoxical findings have been reported in patients with prevalent heart failure and known CV disease, as high levels of circulating adiponectin have been associated with poorer prognosis (13-16).

Only relatively few studies have addressed the role of adiponectin in CAD, and data on the association between this adipokine on LV function and remodeling are lacking. The GIPS-III trial was designed to assess the efficacy of metformin, an oral anti-diabetic drug, on LV ejection fraction (LVEF) in patients presenting with ST segment elevation myocardial infarction (STEMI) and treated with primary percutaneous coronary intervention (PCI). The aim of this substudy was to elucidate the relationship between adiponectin concentration, measured during the acute phase and at 4 months post MI, and LV function and remodeling. We also investigated the effect of metformin treatment on this relationship.

METHODS

Study design

This study is a post-hoc sub-analysis of the Glycometabolic Intervention as adjunct to Primary Percutaneous Intervention in ST Elevation Myocardial Infarction (GIPS)-III Trial. The GIPS-III trial is a prospective, single center, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of metformin treatment on preservation of LVEF in patients presenting with STEMI without diabetes. The design and outcomes have been previously reported (17,18). Briefly, consecutive patients with a first STEMI who were

admitted to the University Medical Center Groningen between January 1, 2011, and May 26, 2013, were eligible for this trial. All patients received standard medical treatment for a STEMI, including dual anti-platelet therapy, statin, beta blocker, and an ACE inhibitor, unless contraindicated. Inclusion criteria included age of 18 years or more, and the presence of STEMI for which primary PCI was performed with implantation of a minimum of one stent of a 3.0 mm diameter. Patients were considered ineligible based on previous myocardial infarction, known diabetes mellitus, severe renal dysfunction (defined as eGFR < 30 mL/min), candidacy for coronary artery bypass graft surgery, contraindications for magnetic resonance imaging (MRI), as well as an inability to comply with the study protocol and failure to provide informed consent.

This study complies with the Declaration of Helsinki and was approved by the local medical ethics committee (Groningen, The Netherlands).

Study procedures

The study procedures have been described in detail (17,18). During the primary PCI procedure, 380 patients provided verbal consent (1 withdrew), and immediately following coronary intervention, were randomly assigned in a 1:1 ratio to receive either metformin hydrochloride (500 mg) or a visually-matching placebo, both administered twice daily. The study medication was initiated immediately upon arrival at the Coronary Care Unit (CCU), and the first dose was administered within 3 hours of PCI. Written informed consent was provided during the first day after primary PCI.

Following admission to the CCU, blood pressure and heart rate were measured, body weight and height were self-reported, and body mass index (BMI) was calculated. A detailed history that included cardiovascular risk profile was obtained from the patient. Blood was sampled during PCI for assessment of regular chemistry and markers of interest. Standard chemistry measures included blood glucose, glycated hemoglobin (HbA1c), insulin, creatinine, and lipid profile, as well as NT-proBNP, troponin, and creatine kinase (CK). All patients were prescribed standard medication according to current guidelines, offered cardiac rehabilitation programs, as well as received counseling on diet, smoking, and lifestyle modification. Patients were assessed at baseline and at 4 months following discharge. Standard and specialized laboratory assessments were repeated at 4 months.

Cardiac magnetic resonance imaging

The primary efficacy measure of the GIPS-III was LVEF determined by MRI at 4 months post infarction. Cardiac MRI was performed with a 3.0 Tesla whole-body MRI scanner (3 T Achieva, Philips, Best, The Netherlands) at the NeuroImaging Center, Groningen, The Netherlands. To assess LVEF, endocardial and epicardial borders were identified and traced in captured end-systolic and end-diastolic images. MRI data were evaluated by an independent core laboratory, Image Analysis Center, VU University Medical Center, Amsterdam, The Netherlands, and were blinded for randomization status and clinical patient data.

Measurement of adiponectin

Blood samples for adiponectin were obtained during PCI from the femoral vein, collected into EDTA tubes, and were immediately centrifuged, aliquoted, and stored at -80°C. Total plasma adiponectin was analysed using a commercially available enzyme-linked immunosorbent assay (ELISA), (Human Total Adiponectin/Acrp30 Quantikine ELISA kit; R&D Systems). The inter-assay precision (coefficient of variation) for the adiponectin assay was less than 7%.

Statistical analysis

Continuous variables are presented as means ± standard deviation (SD) for normally distributed data, and differences were calculated using the two-sample t-test. Non-normally distributed continuous data are expressed as median values [interquartile range] (IQR), and differences were calculated using the Wilcoxon rank-sum test. Differences in categorical values were calculated using Pearson's chi-square test. The reported P-values are two-sided, and a P-value of < 0.05 was considered statistically significant. All analyses were performed using STATA version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

In the GIPS-III study, the effect of 4 month metformin treatment on the primary efficacy end point, LVEF, was neutral (18). In this secondary analysis, the effect of metformin on adiponectin levels, and their association with parameters of cardiac function and remodeling are investigated.

Baseline characteristics of patients stratified to adiponectin levels

From 308 patients, both baseline and 4 month samples were available for plasma adiponectin measurement, and were considered for this sub-analysis. The mean age was 58 ± 11 years, and 79% were male. Adiponectin levels ranged from 2,443 to 10,024 ng/ml, with a median value of 5,057 (IQR: 3,325 – 7,596) ng/ml. Baseline characteristics of patients stratified by median adiponectin concentration are presented in Table I. Demographic data indicated that patients with above median adiponectin levels were more often female ($P<0.001$), and presented with lower BMI scores ($P=0.007$) and higher diastolic blood pressure ($P=0.002$). Plasma adiponectin levels were positively associated with NT-proBNP levels ($P<0.001$) and inversely with creatinine ($P=0.043$). The presence of other conventional cardiovascular risk factors such as hypertension or hypercholesterolemia as well as smoking habits showed no significant association with adiponectin levels. Patients with increased adiponectin levels were less likely to develop diabetes mellitus within 4 months ($P=0.006$). Medication profile at discharge was comparable for patients with above or below median adiponectin concentration (Supplemental Table I). Patients with below median levels of adiponectin more often received metformin than patients with above median levels ($P=0.009$; Table I).

Table I. Baseline Characteristics

Characteristic	Total (n=308)	Baseline adiponectin < median (n=154)	Baseline adiponectin > median (n=154)	P value*
Demographics				
Age (years)	58 (11)	57 (12)	59 (11)	0.091
Gender (% male)	243 (79%)	136 (88%)	107 (70%)	**<0.001**
Body mass index (kg/m^2)	26.6 (24.2, 29.4)	27.4 (25.1, 29.4)	25.5 (23.7, 29.4)	**0.007**
Systolic blood pressure (mmHg)	133 (23)	131 (22)	136 (23)	0.050
Diastolic blood pressure (mmHg)	84 (15)	82 (14)	87 (15)	**0.002**
Heart rate (beats/min)	75 (64, 84)	73 (63, 83)	76 (67, 87)	0.063
Cardiovascular risk profile				
Hypertension	87 (28%)	46 (30%)	41 (27%)	0.53
Hypercholesterolemia	190 (62%)	95 (62%)	95 (62%)	1.00
Active smoker at randomisation	167 (54%)	83 (54%)	84 (55%)	0.91
Diabetes mellitus within 4 months	51 (17%)	35 (23%)	16 (11%)	**0.006**
Laboratory parameters				
Creatinine (µmol/L)	73 (64, 82)	75 (66, 83)	71 (61, 80)	**0.043**
Glucose (mmol/L)	8.2 (7.0, 9.6)	8.5 (7.1, 9.7)	8.1 (7.0, 9.5)	0.23
NT-proBNP (ng/L)	74 (37, 179)	59 (32, 136)	86 (51, 238)	**<0.001**
HbA1c (%)	5.8 (5.6, 6.0)	5.8 (5.6, 6.1)	5.7 (5.6, 6.0)	0.10
CK total (U/L)	129 (86, 207)	133 (86, 215)	126 (84, 192)	0.54
CK-MB (U/L)	16 (13, 23)	16 (13, 24)	16 (13, 22)	0.66
Adiponectin (ng/ml)	5,057 (3,325, 7,596)	3,325 (2,443, 4,003)	7,596 (6,072, 10,024)	**<0.001**
Randomisation treatment (metformin, %)	153 (50%)	88 (57%)	65 (42%)	**0.009**

Values are numbers (%) or medians (IQR) for continuous variables. The age and blood pressure are mean ± S.D.
P values* represent trends for low or high adiponectin.

Effect of metformin on adiponectin levels

Characteristics of patients in both the metformin and placebo groups were well-balanced in terms of age, gender, BMI, cardiovascular risk profile, and treatment at discharge (metformin group, n=153; placebo group, n=155), and these data are presented in Supplemental Table II. At baseline, no significant differences were observed for median adiponectin levels between the placebo group, 5,605 ng/ml (IQR: 3,490 – 7,643) and the metformin group, 4,503 ng/ml (IQR: 3,101 – 7,411) (P=0.087). Four month treatment with metformin significantly lowered circulating adiponectin levels compared to placebo (-629 versus -166, respectively; P=0.026) (Figure 1).

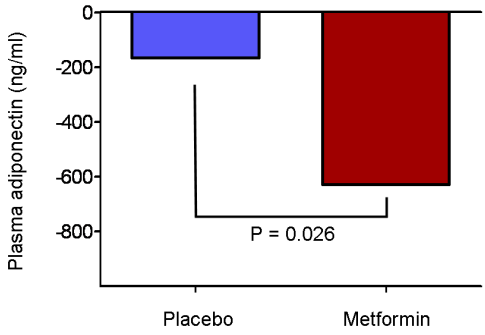

Figure 1
Change in plasma adiponectin concentration with 4 month metformin treatment.

Relationship among adiponectin, metformin treatment, and left ventricular function

To describe the relation between adiponectin levels and metformin or placebo use, we divided the study population on metformin and placebo into above and below median adiponectin levels. Cardiac function and clinical characteristics were assessed in the acute phase (Table II) and at 4 months follow up (Table III).

At baseline, adiponectin concentration did not associate with the primary end point, LVEF, in either placebo- or metformin-treated groups (Figure 2). Further, no significant differences were observed for patients with above median versus below median adiponectin levels for other MRI parameters, including LV end-diastolic mass (LVEDM), LV end-diastolic volume (LVEDV), and infarct size, assessed with late gadolinium enhancement, as well as angiographic procedural characteristics occurring within 4 months. Clinical outcomes are presented, but no analyses were performed (Table II).

Similarly, no association was observed between indices of cardiac function and remodeling and adiponectin levels measured at 4 months after myocardial infarction in placebo or metformin groups, except for LVEDM, where high adiponectin levels was found to be inversely correlated in patients treated with metformin. The relationship between adiponectin levels, measured in the placebo versus metformin group at baseline and 4 months, and LVEF and infarct size are shown in Figures 2 and 3, respectively.

In further exploratory analyses, we divided subjects according to infarct size, which was defined using the 90th percentile as a cut-off point. Baseline adiponectin levels did not show any significant relation to infarct size (Figure 4A). In contrast, there was a clear relationship for infarct size and future LV remodeling as patients presenting with the largest infarct size demonstrated significantly greater increases in LVEDV compared to patients with smaller infarct size (P<0.001) (Figure 4B). It is therefore unlikely that adiponectin is involved in the response to acute MI.

Table II. Baseline Cardiac Functional Measures and Clinical Characteristics

		Placebo			Metformin		
		Low adiponectin	High adiponectin		Low adiponectin	High adiponectin	
	Total	< 5,605	> 5,605		< 4,503	> 4,503	
Characteristic	(n=308)	(n=78)	(n=77)	P value*	(n=77)	(n=76)	P value*
MRI measurements							
LVEF (%)	55.5 (50.2, 59.8)	55.9 (51.6, 60.0)	56.7 (51.3, 59.7)	0.63	53.7 (50.3, 59.8)	55.7 (46.7, 60.3)	0.91
LVEDM (g)	101 (86, 116)	101 (86, 117)	96 (84, 115)	0.49	102 (93, 117)	101 (84, 115)	0.20
LVESV (ml)	84 (66, 104)	82 (69, 99)	83 (62, 100)	0.39	82 (69, 109)	87 (63, 111)	0.78
LVEDV (ml)	189 (163, 219)	189 (168, 218)	183 (159, 220)	0.53	192 (168, 218)	188 (154, 221)	0.49
Infarct Size (% of LV)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.79	0.1 (0.0, 0.1)	0.1 (0.0, 0.2)	0.077
PCI characteristics							
Ischemic time (min)	158 (108, 244)	154 (109, 218)	149 (105, 236)	0.93	157 (103, 255)	163 (112, 259)	0.75
Single vessel disease (%)	216 (70%)	58 (74%)	55 (71%)		46 (60%)	57 (75%)	**0.044**
LAD culprit lesion (%)	119 (39%)	29 (37%)	29 (38%)	0.82	28 (36%)	33 (43%)	0.64
TIMI flow (%)							
0	173 (56%)	45 (58%)	48 (62%)	0.69	37 (48%)	43 (57%)	0.74
1	25 (8%)	5 (6%)	7 (9%)		7 (9%)	6 (8%)	
2	51 (17%)	8 (10%)	8 (10%)		20 (26%)	15 (20%)	
3	59 (19%)	20 (26%)	14 (18%)		13 (17%)	12 (16%)	
Myocardial blush grade (%)							
0	6 (2%)	2 (3%)	2 (3%)	0.36	0 (0%)	2 (3%)	0.34
1	19 (6%)	2 (3%)	6 (8%)		4 (5%)	7 (9%)	
2	66 (22%)	15 (19%)	19 (25%)		18 (24%)	14 (19%)	
3	214 (70%)	59 (76%)	50 (65%)		54 (71%)	51 (69%)	
Clinical outcomes within 4 months							
STEMI (%)	1 (0.3%)	1 (1%)	0 (0%)				
Non-STEMI (%)	5 (2%)	0 (0%)	1 (1%)		2 (3%)	2 (3%)	
Re-infarction (%)	6 (2%)	1 (1%)	1 (1%)		2 (3%)	2 (3%)	
MACE#	7 (2%)	1 (1%)	1 (1%)		3 (4%)	2 (3%)	
Diabetes mellitus (%)	51 (17%)	18 (23%)	7 (9%)		15 (20%)	11 (14%)	

Values are numbers (%) or medians (IQR) for continuous variables. P values* represent trends for low or high adiponectin. MACE# includes death, re-infarction, or target lesion revascularization.

Table III. Cardiac Functional Measures and Clinical Characteristics at 4 Months Follow Up

		Placebo			Metformin		
		Low adiponectin	High adiponectin		Low adiponectin	High adiponectin	
	Total	< 4,941	> 4,941		< 4,060	> 4,060	
Characteristic	(n=308)	(n=78)	(n=77)	P value*	(n=77)	(n=76)	P value*
MRI measurements							
LVEF (%)	55.5 (50.2, 59.8)	56.2 (52.9, 59.3)	56.2 (51.3, 60.7)	0.72	53.9 (50.4, 59.4)	54.8 (45.5, 60.3)	0.71
LVEDM (g)	101 (86, 116)	103 (88, 123)	92 (83, 112)	0.13	105 (93, 119)	97 (85, 112)	**0.028**
LVESV (ml)	84 (66, 104)	84 (69, 99)	80 (63, 100)	0.37	83 (69, 109)	87 (63, 111)	0.74
LVEDV (ml)	189 (163, 219)	192 (169, 218)	183 (160, 220)	0.27	194 (169, 217)	189 (155, 221)	0.34
Infarct size (g)	7.3 (2.0, 14.1)	7.0 (1.8, 11.7)	8.1 (1.2, 14.2)	0.60	6.7 (1.6, 14.0)	7.7 (2.5, 15.4)	0.62
Infarct Size (% of LV)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.50	0.1 (0.0, 0.1)	0.1 (0.0, 0.1)	0.50

Values are numbers (%) or medians (IQR) for continuous variables. P values* represent trends for low or high adiponectin.

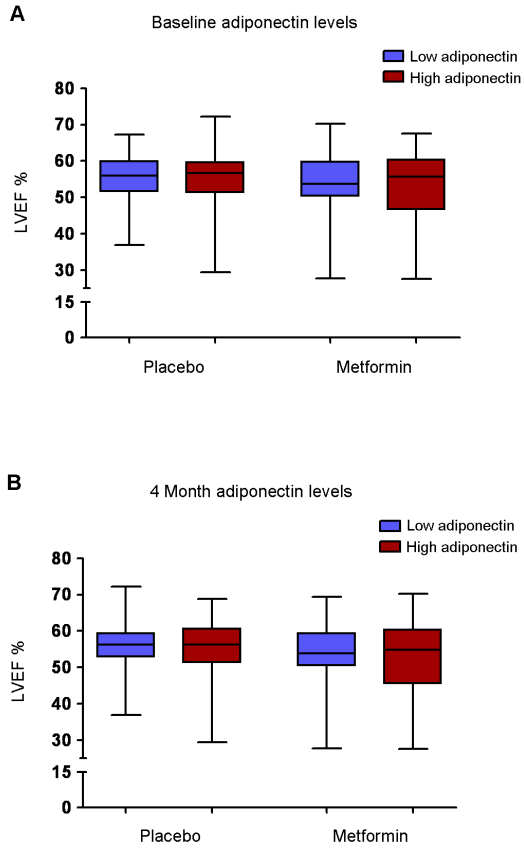

Figure 2
Association between plasma adiponectin levels and left ventricular ejection fraction measured during (**A**) acute MI, and (**B**) at 4 months post MI, in patients randomized to placebo or metformin treatment. Adiponectin levels are above or below median values. Boxes are interquartile ranges.

DISCUSSION

This post-hoc substudy assessed whether adiponectin levels are associated with LV dysfunction and remodeling in STEMI patients treated with PCI. We found no significant relation between circulating adiponectin levels and the primary efficacy end point, LVEF, in both the acute phase and during a stable time point at 4 months post MI. Further, adiponectin levels did not associate with other parameters of cardiac remodeling, including LVEDV and LV mass, nor infarct size. Metformin treatment lowered adiponectin levels at 4 months, but this did not affect LV function, suggesting that adiponectin is not directly involved in post infarction remodeling. Our findings therefore do not support a protective role for adiponectin in the preservation of cardiac function and infarct remodeling in post MI patients.

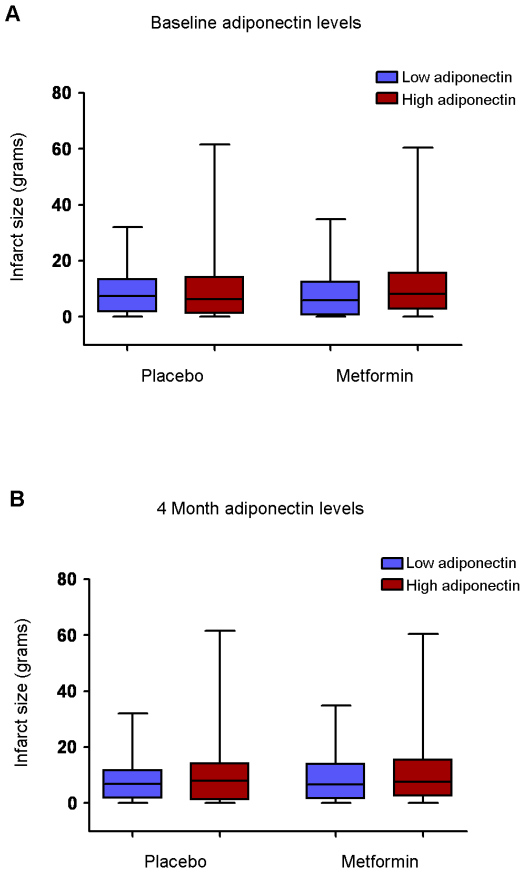

Figure 3
Relationship between adiponectin levels and infarct size assessed in (**A**) acute MI, and (**B**) at 4 months following MI, in patients treated with placebo or metformin. Adiponectin levels are above or below median values. Boxes are interquartile ranges.

Epidemiological studies provide evidence for a protective effect of adiponectin among patients at risk for atherosclerosis and cardiovascular disease. Adiponectin has established functions in lipid metabolism as well as insulin-sensitizing and atheroprotective properties, and since metabolic disorders are closely linked with cardiovascular disease pathogenesis, adiponectin has gained interest in this setting. An inverse relationship has been observed between low adiponectin levels and cardiovascular risk factors, including obesity (3), diabetes (5), and hypertension (19). Further, low adiponectin levels associated with multiple atherosclerotic lesions in coronary arteries (20), and increased the risk for CAD (6). In patients with known CAD, high concentrations of adiponectin correlated with a lower risk for MI (8), and low adiponectin was found to be associated with increased major adverse CV events (21).

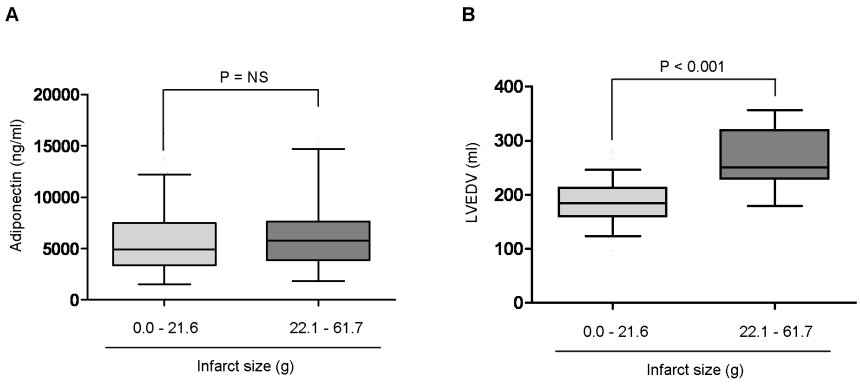

Figure 4
Assessment of left ventricular remodeling in relation to adiponectin levels. (**A**) Baseline adiponectin concentration in relation to infarct size was evaluated using the 90th percentile. (**B**) The effect of infarct size on left ventricular end-diastolic volume (LVEDV).

Despite evidence implicating adiponectin as a protective modifier of cardiovascular risk, results are conflicting regarding patients with known CV disease, as high levels of adiponectin associated with increased mortality (16,22). This raises the question concerning the role of adiponectin in stable versus unstable CAD (14). To date, only few studies have addressed this role in patients who are at high risk, presenting with acute coronary syndromes or acute MI. Wilson et al. investigated the association between adiponectin and cardiovascular events in patients with acute coronary syndrome, and found that higher adiponectin levels independently associated with a higher risk of recurrent cardiovascular events, as well as for heart failure (14). In support of this finding, increased plasma adiponectin independently predicted all-cause and CV mortality in STEMI patients treated with primary PCI (15), whereas hypoadiponectinemia negatively correlated with a major adverse CV event in patients recruited exclusively for acute coronary syndrome (23). More recently, De Roeck et al. investigated the role of adiponectin in ischemia reperfusion (IR) injury in STEMI patients, and found that baseline total adiponectin concentration correlated with IR injury after PCI, however, no significant relation between adiponectin levels and major adverse CV events during one year follow up occurred (24). TIMI myocardial blush grade was also evaluated in this study, by what they defined as IR injury, but adiponectin had no relation on this clinical end point. Our study is underpowered to predict clinical outcome, but is sufficiently powered on other clinical surrogate end points, and we were able to confirm the absence of an effect on both TIMI flow and myocardial blush grade.

Although a positive association between increased adiponectin and poor prognostic outcome has been demonstrated in high risk cohorts, most of these studies examined end points involving clinical outcomes of CV events. However, the relationship among adiponectin and parameters of cardiac function and remodeling in patients with CAD is unknown. In STEMI

patients, LV function is currently regarded as the most important predictor of morbidity and mortality. However, we could not establish any relation between circulating adiponectin and LV function after acute MI, which was assessed with cardiac MRI, a well-established measure of cardiac function. In addition, no relation among infarct size, or other indices of cardiac remodeling was observed, either in the acute phase or at 4 months follow up. These findings are in contrast to that in healthy individuals where high circulating concentrations of adiponectin were inversely and independently related to echocardiographic determinants of LV hypertrophy (10,12), and in preclinical studies, which demonstrated protective effects for adiponectin against the development of systolic dysfunction and loss of myocytes following MI (25).

Based on our functional assessment with MRI, adiponectin appears to be acting on other processes not related to myocyte function or myocardial geometry, and therefore, other clinical end points may need to be considered. Adiponectin exerts protective effects not only in the heart, but also within the vasculature (26), thus it may be exerting a regulatory role in cardiac injury by modulating anti-inflammatory processes, endothelial dysfunction, or vascular remodeling (27), which need to be assessed clinically. It has also been postulated that adiponectin influences plaque stability since low plasma adiponectin strongly predicted vulnerable plaques (28).

In this study, we show that treatment with metformin lowers circulating adiponectin levels. Evidence suggests that metformin has favorable efficacy in heart failure (29), as well as on LV function and remodeling following MI (30,31). However, the GIPS-III trial demonstrated that metformin intervention in STEMI patients was neutral with regard to this outcome (18). Lowering of adiponectin after 4 months metformin treatment had no significant effect on LVEF, infarct size, or remodeling, suggesting that adiponectin is not an acute responder in MI. Interestingly, rapid declines in adiponectin levels after acute MI negatively correlated with plasma CRP, indicating that hypoadiponectinemia is associated with an increased inflammatory response in acute myocardial ischemia (32). This would suggest that the lowering effect of metformin on adiponectin may be disadvantageous. It is not clear why adiponectin levels are significantly decreased by metformin treatment, which is in contrast to studies conducted in diabetic subjects where circulating adiponectin levels are unaltered (33,34). Metformin and adiponectin display several overlapping functions, including regulation of insulin sensitivity via AMPK activation (27), thus metformin may act on adipose tissue to suppress adiponectin production.

Limitations. Three isoforms for adiponectin exist, however, the immunoassay used in this study only assessed total adiponectin levels, and therefore assessment of different molecular isoforms may indicate different clinical outcomes. The follow up period of 4 months was too short to establish whether adiponectin concentration has prognostic implications on cardiovascular risk, or predicts major adverse CV events and mortality. Our results are

confined to a highly selected population representing first time STEMI patients.

Conclusions. In this study, we show that measurement of circulating adiponectin concentrations in acute MI and at 4 month follow up do not associate with LV function, obtained by MRI, and that no relationship exists among adiponectin, infarct size, and cardiac remodeling. Pharmacological modulation of adiponectin levels with metformin had no further effect on LV function, so collectively, these data strongly suggest that adiponectin is not exerting a cardioprotective role. These findings, however, do not preclude a role for adiponectin in mediating other processes related to, for example, inflammation, endothelial dysfunction, and plaque stability.

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CONFLICT OF INTEREST

None.

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Supplemental Table I. Medication History at Discharge

Characteristic	Total (n=308)	Baseline adiponectin < median (n=154)	Baseline adiponectin > median (n=154)	P value*
Aspirin	301 (98%)	151 (98%)	150 (97%)	0.70
Clopidogrel	221 (72%)	116 (75%)	105 (68%)	0.16
Prasugrel	4 (1.3%)	2 (1.3%)	2 (1.3%)	1.00
Ticagrelor	83 (30%)	36 (23%)	47 (31%)	0.16
Coumarine	15 (5%)	5 (3%)	10 (7%)	0.19
Beta-blocker	295 (96%)	146 (95%)	149 (97%)	0.40
ACE-inhibitor or ARB	246 (80%)	123 (80%)	123 (80%)	1.00
Calcium-channel blocker	9 (3%)	4 (3%)	5 (3%)	0.74
Aldosterone receptor antagonist	30 (10%)	16 (10%)	14 (9%)	0.70
Diuretics	6 (2%)	1 (1%)	5 (3%)	0.099
Statins	306 (99%)	154 (100%)	152 (99%)	0.16
Insulin	3 (1.0%)	2 (1.3%)	1 (0.6%)	0.56
Oral antihyperglycemic drugs	3 (1.0%)	1 (0.6%)	2 (1.3%)	0.56

Values are numbers (%) or medians (IQR) for continuous variables. *P* values* represent trends for high or low adiponectin.

Supplemental Table II. Effect of Metformin Treatment Compared with Placebo

Characteristic	Placebo (n=155)	Metformin (n=153)	P value*
Baseline demographics			
Age (years)	59 (11)	57 (12)	0.24
Gender (% male)	118 (76%)	125 (82%)	0.23
Body mass index at baseline (kg/m^2)	26.8 (24.4, 29.4)	26.5 (24.2, 29.4)	0.76
Systolic blood pressure (mmHg)	133 (23)	134 (22)	0.67
Diastolic blood pressure (mmHg)	84 (15)	85 (15)	0.35
Cardiovascular risk profile			
Hypertension	46 (30%)	41 (27%)	0.53
Hypercholesterolemia	104 (67%)	86 (56%)	**0.049**
Current smoking	78 (50%)	89 (58%)	0.17
Cerebrovascular accident	1 (0.6%)	1 (0.7%)	0.99
Previous PCI	3 (1.9%)	1 (0.7%)	0.32
Laboratory parameters			
Creatinine at baseline (µmol/L)	73 (64, 80)	72 (62, 85)	0.85
Creatinine at 4 months (µmol/L)	80 (72, 89)	79 (70, 87)	0.56
HbA1c at baseline (%)	5.8 (5.6, 6.0)	5.8 (5.6, 6.1)	0.80
HbA1c at 4 months (%)	5.9 (5.7, 6.1)	5.9 (5.6, 6.1)	0.11
CK total at baseline (U/L)	123 (82, 183)	133 (91, 246)	0.065
CK total at 4 months (U/L)	89 (77, 115)	59 (52, 84)	0.29
Glucose at baseline (mmol/L)	8.1 (7.0, 9.6)	8.2 (7.0, 9.5)	0.93
Glucose at 4 months (mmol/L)	5.6 (5.2, 6.1)	5.6 (5.1, 6.2)	0.69
NT-proBNP at baseline (ng/L)	68 (36, 177)	74 (37, 183)	0.81
NT-proBNP at 4 months (ng/L)	166 (74, 355)	165 (69, 389)	0.56
Adiponectin at baseline (ng/mL)	5,605 (3,490, 7,643)	4,503 (3,101, 7,411)	0.087
Adiponectin at 4 months (ng/mL)	4,941 (3,120, 7,354)	4,060 (2,343, 6,409)	**0.012**
Concomitant therapies at discharge			
Beta blocker	152 (98%)	143 (94%)	**0.045**
ACE inhibitor or ARB	116 (75%)	130 (85%)	**0.027**
Aldosterone receptor antagonist	11 (7%)	19 (12%)	0.12
Diuretics	2 (1%)	4 (3%)	0.40
Statins	154 (99%)	152 (99%)	0.99
Insulin	1 (1%)	2 (1%)	0.55
Oral anti-hyperglycemic drugs	2 (1%)	1 (1%)	0.57

Values are numbers (%) or medians (IQR) for continuous variables. The age and blood pressure are mean ± S.D. *P* values* represent trends.

Supplemental Table III. Patient Demographics and Laboratory Measures at Baseline

	Placebo			Metformin		
Characteristic	Low adiponectin < 5,605 (n=78)	High adiponectin > 5,605 (n=77)	P value*	Low adiponectin < 4,503 (n=77)	High adiponectin > 4,503 (n=76)	P value*
Demographics						
Age (years)	58 (12)	60 (11)	0.22	57 (11)	58 (12)	0.41
Gender (% male)	66 (85%)	52 (68%)	**0.013**	71 (92%)	54 (71%)	**<0.001**
Body mass index (kg/m^2)	28.0 (25.2, 29.4)	25.4 (23.6, 28.6)	**0.006**	26.6 (24.7, 29.2)	26.1 (23.6, 29.5)	0.42
Systolic blood pressure (mmHg)	131 (22)	134 (25)	0.39	130 (23)	138 (21)	**0.015**
Diastolic blood pressure (mmHg)	82 (15)	85 (15)	0.15	82 (14)	88 (15)	**0.006**
Heart rate (beats/min)	71 (60, 83)	77 (68, 88)	**0.016**	75 (64, 83)	76 (64, 86)	0.82
Laboratory parameters						
Creatinine (µmol/L)	74 (66, 81)	72 (62, 79)	0.15	74 (65, 85)	71 (59, 85)	0.35
Glucose (mmol/L)	8.6 (7.3, 10.1)	8.0 (7.0, 9.6)	0.21	8.3 (7.0, 9.4)	8.2 (6.9, 9.5)	0.86
NT-proBNP (ng/L)	61 (32, 174)	84 (49, 177)	0.092	59 (33, 115)	104 (51, 272)	**0.009**
HbA1c (%)	5.9 (5.6, 6.1)	5.7 (5.6, 5.9)	**0.008**	5.8 (5.6, 6.1)	5.8 (5.6, 6.1)	0.80
CK total (U/L)	123 (83, 178)	123 (82, 183)	0.87	143 (93, 265)	128 (88, 224)	0.32
CK-MB (U/L)	16 (12, 23)	16 (13, 22)	0.95	17 (13, 25)	16 (13, 28)	0.86
Adiponectin (ng/ml)	3,494 (2,792, 4,193)	7,643 (6,383, 9,980)	**<0.001**	3,101 (2,044, 3,764)	7,528 (5,715, 10,076)	**<0.001**

Values are numbers (%) or medians (IQR) for continuous variables. The age and blood pressure are mean ± S.D. *P* values* represent trends.